IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:	Shehada *et al.*
Patent No.	6,124,597
Issued:	September 26, 2000
For:	**METHOD AND DEVICES FOR LASER INDUCED FLUORESCENCE ATTENUATION SPECTROSCOPY**

CERTIFICATE OF EXPRESS MAILING

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PRELIMINARY AMENDMENT AND STATEMENT OF STATUS OF THE CLAIMS AND SUPPORT FOR CLAIM CHANGES UNDER 37 C.F.R. § 1.173 FOR REISSUE APPLICATION

BOX REISSUE
Assistant Commissioner for
Patents
Washington, D. C. 20231

Dear Sir/Madam:

The purpose of this reissue application is to correct defects in the above-captioned patent issued on September 26, 2000, under 35 U.S.C. § 251 and 37 C.F.R. § 1.171, et. seq. In connection with the above-captioned patent the Examiner is respectfully requested to consider the following amendment and the Applicant's corresponding remarks contained herein. Applicant's Statement of the Status of the Claims and Support for Claim Changes is found in Applicant's Remarks.

AMENDMENTS

Brackets to signify a deletion are in bold to differentiate them from non-bolded brackets that are to remain as proper text of the specification.

In the Specification:

Please delete Figures 11-16 and insert therefor the formal drawings Figures 11-16, submitted with this application.

At column 2, line 63, through column 3, line 17, please amend the paragraph as follows:

--Ischemia and hypoxia are both conditions that deprive tissue of oxygen, leading to anaerobic metabolism and the accumulation of the metabolic coenzyme NADH. The coenzyme NADH is a fluorescent molecule. Therefore, ischemia and hypoxia can be indirectly detected using LIF techniques by sensing increased concentrations of NADH and interpreting its elevation as a sign of oxygen deficiency. A common indicator of oxygen deficiency is the ratio between the LIF intensity at wavelengths associated with the peak fluorescence emission of NADH, collagen and elastin. However, such methods have not been practically applied for the detection of ischemia because of several complications. First, these methods cannot determine whether the elevated NADH concentration is caused by ischemia, hypoxia or hypermetabolism. Second, scarred or fibrosed tissue would be detected as normal because of their low NADH concentration. Finally, the indicator ratios are calculated by normalizing the intensity of NADH peak fluorescence by that of collagen or elastin. Although the fluorescence of the structural proteins elastin and collagen does not vary with tissue oxygenation, their fluorescence **[**vary**]** varies with the site of measurement.--.

At column 5, lines 6-9, please amend the paragraph as follows:

--FIGS. **9**(*a*)-(*c*) are partial perspective views of three LIFAS probes having waveguides arranged in different geometrical configurations adapted for different applications (top row is an elevation view; middle row is a side view; bottom row is a bottom view);--.

At column 9, lines 47-64, please amend the paragraph as follows:

--In addition, the signals **224***a* and **225***a* will also exhibit wavelength-dependent modulations caused by the instrumental effects. The wavelength-dependent modulations due to the instrumental effects can be determined and, in turn, compensated for by conducting a calibration of the LIFAS system **210**. System calibration can be performed using light from a standard lamp (Quartz Halogen Lamp, Model No. 63358, Oriel Instruments, Stratford, Conn.) having a predetermined continuous spectrum to measure the wavelength-dependent instrumental effects of the LIFAS system **210**. Once these instrumental effects are known, the processor **223** can be adapted to correct the measured intensities $I_{c1}(\lambda)$ and $I_{c2}(\lambda)$ for modulations caused by the wavelength-dependent instrumental effects. The corrected intensities $I_{c1}(\lambda)^c$ and $I_{c2}(\lambda)^c$ representing the intensity of the first and second portions **228** and **230** of the return light **220** at different wavelengths can then be used to determine the attenuation coefficient $\alpha(\lambda)$ of the sample **214** as described below.--.

At column 10, lines 45-61, please amend the paragraph as follows:

--Whether the measured attenuation accounts for absorption and/or scattering is mainly determined by the wavelength band of interest and the nature of the sample. The optical properties of biological tissue and the effects of tissue on LIF are greatly different for the wavelengths below and above approximately 600 nm. Below about 600 nm, the optical attenuation of biological tissue is primarily due to absorption and, hence, the attenuation coefficient $\alpha(\lambda)$ will represent absorptivity

[$\alpha(\lambda)$] $\underline{a(\lambda)}$. Absorptivity is a property of a substance, while absorbance is a property of a particular sample of a substance. Therefore, absorbance will vary with the concentration of the substance (e.g., hemoglobin) and geometry of the tip of the probe. Thus, for samples such as biological tissue where the attenuation of the sample is primarily due to absorption, the absorbance $A(\lambda)$ and the percent transmittance $\%T(\lambda)$ of the sample can be calculated as follows:--.

At column 13, line 10, please amend equation (10) as follows:

-- $\alpha(\lambda) = \{1/y^3\} \ln\{I_{[cx]\underline{xc}}(\lambda)^c/I_{co}(\lambda)^c\}$ --.

At column 13, lines 29 - 37, please amend the paragraph as follows:

-- As discussed in connection with the previous embodiment, the measured attenuation may account for absorption and/or scattering depending on the wavelength band of interest and the nature of the sample. Below about 600 nm, the optical attenuation of biological tissue is primarily due to absorption and, hence, the attenuation coefficient $\alpha(\lambda)$ will represent absorptivity [$\alpha(\lambda)$] $\underline{a(\lambda)}$. Also, the absorbance $A(\lambda)$ and the percent transmittance $\%T(\lambda)$ of such samples can be calculated as follows: --.

At column 16, line 49, through column 17, line 7, please amend the paragraph as follows:

--FIG. **9** shows three alternative geometrical configurations of the collection-only optical fibers **[950]**$\underline{\textbf{450'}}$*a-h* about the excitation-collection waveguide **[946]**$\underline{\textbf{446'}}$. In these embodiments, it is desirable to couple each of the collection-only waveguides **[950]**$\underline{\textbf{450'}}$*a-h* to a separate sensor so that the intensity of each portion of the return light collected by each fiber can be monitored. In FIG. **9**(*a*), the collection-only waveguides **[950]**$\underline{\textbf{450'}}$*a-h* are arranged about the excitation-collection waveguide **[946]**$\underline{\textbf{446'}}$ so that their apertures have a helical configuration.

Because the aperture of each successive collection-only waveguide is shifted axially away from the aperture **[947]**__447'__ of the excitation-collection waveguide **[946]**__446'__, the return light collected by each of the collection-only waveguides **[950]**__450'__*a-h* will be attenuated in varying degrees. Use of a probe arrangement having a plurality of collection distances will be useful in measuring the polarization and/or the attenuation of, especially, a sample having a higher sensitivity to attenuation due to absorption. Furthermore, a probe incorporating a plurality of collection distances [have] __has__ application to a larger variety of samples. For example, where the sample is highly attenuating, the collection-only waveguides having apertures close to the excitation site can be used to collect the return light. Where the sample is lightly attenuating, the return light collected by the waveguides having apertures that are further from the excitation site will be useful in determining the attenuation.--.

At column 17, lines 8-18, please amend the paragraph as follows:

--In FIG. **9**(*b*), the collection-only waveguides **[950]**__450'__*a-c* are displaced laterally with respect to the excitation-collection waveguide **[946]**__446'__. Such a probe configuration will be useful in measuring the polarization and/or the attenuation of the sample where the sample has a higher sensitivity to attenuation due to scattering. The return light collected by the waveguide **[950]**__450'__*c* will be useful in measuring attenuation of a lightly attenuating sample. On the other hand, the return light measured by the closest waveguide **[950]**__450'__*a* will be useful in measuring the attenuation of a heavily-attenuating sample.--.

At column 17, lines 19-23, please amend the paragraph as follows:

--In FIG. **9**(*c*), the collection-only waveguides **[950]**__450'__*a-c* are both axially and laterally displaced with respect to the excitation-collection waveguide **[946]**__446'__. This configuration combines the advantages of both of the aforementioned configurations shown in FIGS. **9**(*a*) and **9**(*b*).--.

At column 18, lines 30-57, please amend the paragraph as follows:

--Another parameter found to be useful in the classification of normal, ischemic and hypoxic tissue, is the intensity of return light from a pair of LIFAS collection pathways (i.e., $[I_{c1}(\lambda)^c, I_{c2}(\lambda)^c]$ or $[I_{xc}(\lambda)^c, I_{co}(\lambda)^c]$ for the LIFAS embodiments described above[.]). For example, FIG. **13** shows the $[I_{xc}(\lambda)^c, I_{co}(\lambda)^c]$ pair at λ=480 nm, symbolized as $[I_{xc}(480)^c, I_{co}(480)^c]$, measured from hyper-oxygenated (x), normal (o) and oxygen deficient (+) rabbit kidney. The $[I_{xc}(480)^c, I_{co}(480)^c]$ from normal and oxygen-deficient tissue tend to cluster in two linearly separable regions of the two dimensional $I_{xc}(\lambda)^c$-$I_{co}(\lambda)^c$ space. Thus, a simple linear or nonlinear classifier function can be trained on a set of $[I_{xc}(\lambda)^c$**[c]**, $I_{co}(\lambda)^c]$ pairs measured using a LIFAS system from normal, ischemic and hypoxic tissue. Other classifiers such as artificial neural networks (ANN) are also being used. The trained classifier function can then be used to classify an unknown $[I_{xc}(\lambda)^c, I_{co}(\lambda)^c[\ ]]$ pair as normal, ischemic or hypoxic. A "nearest neighbor" (NN) classifier has been found to perform satisfactorily. The NN classifier checks the proximity of an unknown $[I_{xc}(480)^c, I_{co}(480)^c]$ pair to clusters of predetermined $[I_{xc}(480)^c, I_{co}(480)^c]$ pairs measured from known normal, ischemic and hypoxic tissue. Other classifiers such as artificial neural networks (ANN) can also be utilized. For myocardial and renal tissue it has been found that it is preferable to use $[I_{xc}(\lambda)^c, I_{co}(\lambda[^c])^c]$ measured at 480 nm, to optimize signal-to-noise ratio. However, $[I_{xc}(\lambda)^c, I_{co}(\lambda)^c]$ at other single or multiple pre-selected wavelengths can also be used.--.

At column 18, line 58 through column 19, line 15, please amend the paragraph as follows:

--An additional parameter for the classification of normal, ischemic and hypoxic tissue, is the wavelength of the peak transmittance of the tissue, symbolized hereafter as $\lambda_{max\text{-}T}$, especially in the 450-500 nm band. An alternative to $\lambda_{max\text{-}T}$ is the wavelength of the peak $I_{co}(\lambda)^c$ in the 450-500 nm band, symbolized hereafter as $\lambda_{max\text{-}co}$. Both $\lambda_{max\text{-}T}$ and $\lambda_{max\text{-}co}$ shift towards

shorter wavelengths as the hemoglobin in the tissue becomes deoxygenated. For example, FIG. **14** shows $I_{co}(\lambda)^c$ spectra that are acquired using the LIFAS system shown in FIG. **10** employing 308 nm excitation radiation produced by an[d] XeCl excimer laser. It should be noted that the $\lambda_{max\text{-}co}$ of normal tissue shifts to a shorter wavelength as the tissue becomes hypoxic; whereas the $\lambda_{max\text{-}co}$ of normal tissue shifts to a longer wavelength as the tissue becomes hyperoxic. Specifically, $\lambda_{max\text{-}co}$ varies between about 480 and 500 nm as blood or hemoglobin oxygenation varies between deoxygenated to oxygenated, respectively. A separation border can be identified at about 489.5 nm to separate $\lambda_{max\text{-}co}$ of normal tissue (peaks above 489.5 nm) from hypoxic/ischemic tissue (peaks below 489.5 nm). A simple classifier can be trained to identify tissue as hypoxic if its $\lambda_{max\text{-}co}$ is below 489.5, and vice versa. The degree of hypoxia is determined from the magnitude of the shift in $\lambda_{max\text{-}co}$ from the normal value, the smaller the shift, the subtler the hypoxia.--.

In the Claims:

1.(Amended) A spectroscopic method of analyzing a sample, comprising:

irradiating a sample with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance; and

comparing the first and second portions of the modulated fluorescence to each other to determine a modulation characteristic of the sample.

20.(Amended) The method of claim [11] 1, wherein the method further includes determining the intrinsic fluorescence of the sample.

38.(Amended) A spectroscopic method for determining the oxygenation of a biological material, comprising:

irradiating a sample of a biological material with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by attenuation of the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance;

comparing the first and second portions of the modulated fluorescence to each other to determine the attenuation of the sample; and

determining oxygenation of the sample using the attenuation of the sample.

40.(Amended) A spectroscopic method for determining the concentration of hemoglobin in a biological material, comprising:

irradiating a sample of a biological material with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by attenuation of the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance;

comparing the first and second portions of the modulated fluorescence to each other to determine the attenuation of the sample; and

determining the concentration of hemoglobin in the sample using the attenuation of the sample.

42.(Amended) A method for determining a physiological characteristic of a biological material, comprising:

irradiating a sample of a biological material with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance; and

comparing the first and second portions of the modulated fluorescence to each other, using a predictive model, to determine a physiological characteristic of the sample.

44.(Amended) A method for determining a physiological characteristic of a biological material, comprising:

irradiating a sample of a biological material with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance;

comparing the first and second portions of the modulated fluorescence to each other to determine a modulation characteristic of the sample; and

processing the modulation characteristic, using a predictive model, to determine a physiological characteristic of the sample.

46.(Amended) Apparatus for analyzing a sample, comprising:

a source adapted to emit radiation that is directed at a sample to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

a first sensor adapted to monitor the fluorescence at a first distance from the sample and generate a first signal indicative of the intensity of the fluorescence;

a second sensor adapted to monitor the fluorescence at a second distance from the sample and generate a second signal indicative of the intensity of the fluorescence, the second distance being different from the first distance; and

a processor associated with the first sensor and the second sensor and adapted to compare the first and second signals to each other to determine a modulation characteristic of the sample.

48.(Amended) Apparatus for analyzing a sample, comprising:

a source adapted to emit radiation that is directed at a sample volume in a sample to produce fluorescence from the sample, such fluorescence including modulated fluorescence resulting from modulation by the sample;

a first sensor adapted to monitor the fluorescence at a first distance from the sample volume and generate a first signal indicative of the intensity of the fluorescence;

a second sensor adapted to monitor the fluorescence at a second distance from the sample volume and generate a second signal indicative of the intensity of the fluorescence, the second distance being different from the first distance; and

a processor associated with the first sensor and the second sensor and adapted to compare the first and second signals to each other to determine a modulation characteristic of the sample.

49.(Amended) Apparatus for determining a modulation characteristic of a biological material, comprising:

a source adapted to emit excitation light;

a first waveguide disposed at a first distance from the sample adapted to transmit the excitation light from the light source to the biological material to cause the biological material to produce fluorescence, and adapted to collect a first portion of the fluorescence;

a first sensor, associated with the first waveguide, adapted to measure the intensity of the first portion of the fluorescence and generate a first signal indicative of the intensity of the first portion of the fluorescence;

a second waveguide disposed at a second distance from the sample adapted to collect a second portion of the fluorescence, the second distance being different from the first distance;

a second sensor, associated with the second waveguide, adapted to measure the intensity of the second portion of the fluorescence and generate a second signal indicative of the intensity of the second portion of the fluorescence; and

a processor adapted to compare the first and second signals to each other to determine a modulation characteristic of the biological material.

50.(Amended) Apparatus for analyzing a sample, comprising:

a source adapted to emit radiation that is directed at a sample volume in a sample to produce fluorescence from the sample, such fluorescence including modulated fluorescence resulting from modulation by the sample;

a first sensor, displaced by a first distance from the sample volume adapted to monitor the fluorescence and generate a first signal indicative of the intensity of the fluorescence; [and]

a second sensor, displaced by a second distance from the sample volume adapted to monitor the fluorescence and generate a second signal indicative of the intensity of fluorescence, the second distance being different from the first distance; and

a processor associated with the first sensor and the second sensor and adapted to compare the first and second signals to each other to determine a physiological property of the sample.

51.(Amended) Apparatus for determining a physiological property of a biological material, comprising:

a source adapted to emit excitation light;

a first waveguide disposed at a first distance from the sample, and adapted to transmit the excitation light from the light source to the biological material to cause the biological material to produce fluorescence, and further adapted to collect a first portion of the fluorescence;

a first sensor, associated with the first waveguide, for measuring the intensity of the first portion of the fluorescence and generating a first signal representative of the intensity of the first portion;

a second waveguide disposed at a second distance from the sample, and adapted to collect a second portion of the fluorescence, the second distance being different from the first distance;

a second sensor, associated with the first waveguide, for measuring the intensity of the second portion of the fluorescence and generating a second signal representative of the intensity of the second portion; and

a processor adapted to compare the first and second signals to each other to determine a physiological property of the biological material.

52.(Amended) A spectroscopic method of analyzing a sample, comprising:

irradiating a sample with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance;

comparing the first and second portions of the modulated fluorescence to each other to determine a modulation characteristic of the sample;

wherein the sample is a biological tissue [material];

wherein the method further includes determining a physiological property of the tissue using the modulation characteristic; and

wherein the physiological property of the tissue is ischemia.

53.(Amended) A method for determining a physiological characteristic of a biological material, comprising:

irradiating a sample of a biological material with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first distance from the sample;

monitoring a second portion of the modulated fluorescence at a second distance from the sample, the second distance being different from the first distance; and

comparing the first and second portions of the modulated fluorescence to each other, using a predictive model, to determine a physiological characteristic of the sample[;].

wherein the predictive model is multivariate.

54.(Amended) A spectroscopic method of analyzing a sample, comprising:

irradiating a sample with radiation to produce fluorescence from the sample, wherein the fluorescence is modulated by the sample;

monitoring a first portion of the modulated fluorescence at a first angle from the sample;

monitoring a second portion of the modulated fluorescence at a second angle from the sample; and

comparing the first and second portions of the modulated fluorescence to each other to determine a modulation characteristic of the sample.

REMARKS

Deletion of current Figures 11-16 are marked in red in the copy of the printed patent Applicant has provided herewith. Applicant has submitted herewith new formal drawings of Figures 1-17 as they should appear in the reissue patent. The substitution of new Figures 11-16 are supported by Figures 11-16 as originally filed in U.S. Serial No. 08/889,017, on July 7, 1997, a copy of which application is appended as **Exhibit A**. Unfortunately, by clerical error, the wrong drawings of Figures 11-16 were filed as formal drawings during the prosecution of 08/889,017.

The present amendment to Figures 11-16 is also necessary to make Figures 12-16 comport with Brief Description of the Drawings and the references to the figures elsewhere in the text of the specification. Also, it is easily seen that current Figure 13 corresponds to new Figure 12, submitted herewith; current Figure 14 corresponds to new Figure 15, submitted herewith; current Figure 15 corresponds to new Figure 13, submitted herewith; and current Figure 16 corresponds to new Figure 14, submitted herewith.

The amendment at column 3, line 16, is to correct an obvious typographical error.

The amendment at column 5, line 9, are supported in Figure 9 as originally filed.

The amendment at column 9, line 63 is to correct an obvious typographical error.

The amendment at column 10, line 53 is supported in the specification as originally filed, at page 26, line 11. The comma inserted after "e.g.", at column 10, line 56, is merely grammatical.

The amendment at column 13, line 10 is supported in the specification as originally filed, at page 32, line 14.

The amendment at column 13, line 35 is supported in the specification as originally filed, at page 33, line 15.

The amendments of the reference numerals in the three paragraphs at column 16, line 49, through column 17, line 23, are supported in Figure 9(a), Figure 9(b), and Figure 9(c), as originally filed. The comma inserted after "attenuation of", at column 16, line 65, is merely grammatical. The substitution of the word "has" instead of "have", at column 16, line 67, is

merely grammatical.

The amendment at column 18, line 41, is to correct an obvious typographical error, as supported, e.g., at column 18, lines 33, 35, 40, 46, 54, and 55.

The amendments at column 18, lines 32, 34, 38, and 46, are to correct obvious typographical and grammatic errors. The amendment at column 18, line 54 is to correct a typographical error, and is supported, e.g., at column 18, lines 33, 35, 40, 42, 46, and 56.

The amendments at column 19, lines 1 and 14-15, are to correct obvious typographical errors.

Applicant's Statement of the Status of the Claims and Support for Claim Changes

Claims 1-54 are pending. Claims 1, 20, 38, 40, 42, 44, 46, and 48-54 are amended.

The amendment to Claim 1 (pending), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and" is inserted merely for grammatic purpose, at column 23, end of line 5.

The amendment to Claim 20 (pending), was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**).

The amendment to Claim 38 (pending; originally filed as Claim 39), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and" is inserted merely for grammatic purpose at column 25, end of line 2.

The amendment to Claim 40 (pending; originally filed as Claim 41), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and" is now inserted merely for grammatic purpose, at column 25, end of line 35.

The amendment to Claim 42 (pending; originally filed as Claim 48), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and" is inserted merely

for grammatic purpose at column 25, end of line 64.

The amendment to Claim 44 (pending; originally filed as Claim 50), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and", at column 26, end of line 28, and the two commas, at column 26, lines 29 and 30, are inserted merely for grammatic purpose. The commas are supported, for example in Claim 43, at column 26, line 11.

The amendment to Claim 46 (pending; originally filed as Claim 52), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**).

The amendment to Claim 48 (pending; originally filed as Claim 53), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and" is inserted merely for grammatic purpose at column 27, end of line 11.

The amendment to Claim 49 (pending; originally filed as Claim 54), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**); the word "at", at column 27, line 19, the comma at column 27, line 22, and the word "and", at column 27, end of line 36, are inserted merely for grammatic purpose.

The amendment to Claim 50 (pending; originally filed as Claim 55), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The deletion of the word "and", at column 27, line50, and the insertion of the word "and", at column 27, end of line 55, are merely for grammatic purposes.

The amendment to Claim 51 (pending; originally filed as Claim 56), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and", at column 27, line 64; at column 28, line 6; and at column 28, end of line 13; the word "at", at column 27, line 63;

and a comma and the word "further", at column 27, line 66, are all inserted merely for grammatic purpose. The insertion of the word "a" in the preamble, at column 27, line 60, is for greater clarity.

The amendment to Claim 52 (pending; originally filed as Claim 59), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The insertion of the word "a" before the phrase "biological tissue", at column 28, line 32, is for greater clarity. In Claim 52, at column 28, line 32, the substitution of the phrase "biological tissue" instead of "biological material" is for greater clarity and is supported by Claim 52, at column 28, lines 34 and 36.

The amendment to Claim 53 (pending; originally filed as Claim 60), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and", at column 28, end of line 48, and a comma instead of a semi-colon, at column 28, line 51, are inserted merely for grammatic purpose.

The amendment to Claim 54 (pending; originally filed as Claim 61), with respect to comparing ". . . to each other", was submitted in Applicant's Supplemental Amendment, transmitted by Facsimile on March 17, 2000 (**Exhibit B**). The word "and", at column 28, end of line 61, and semi-colons, at column 28, lines 59 and 61, are inserted merely for grammatic purpose.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this reissue application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

By: ____________________
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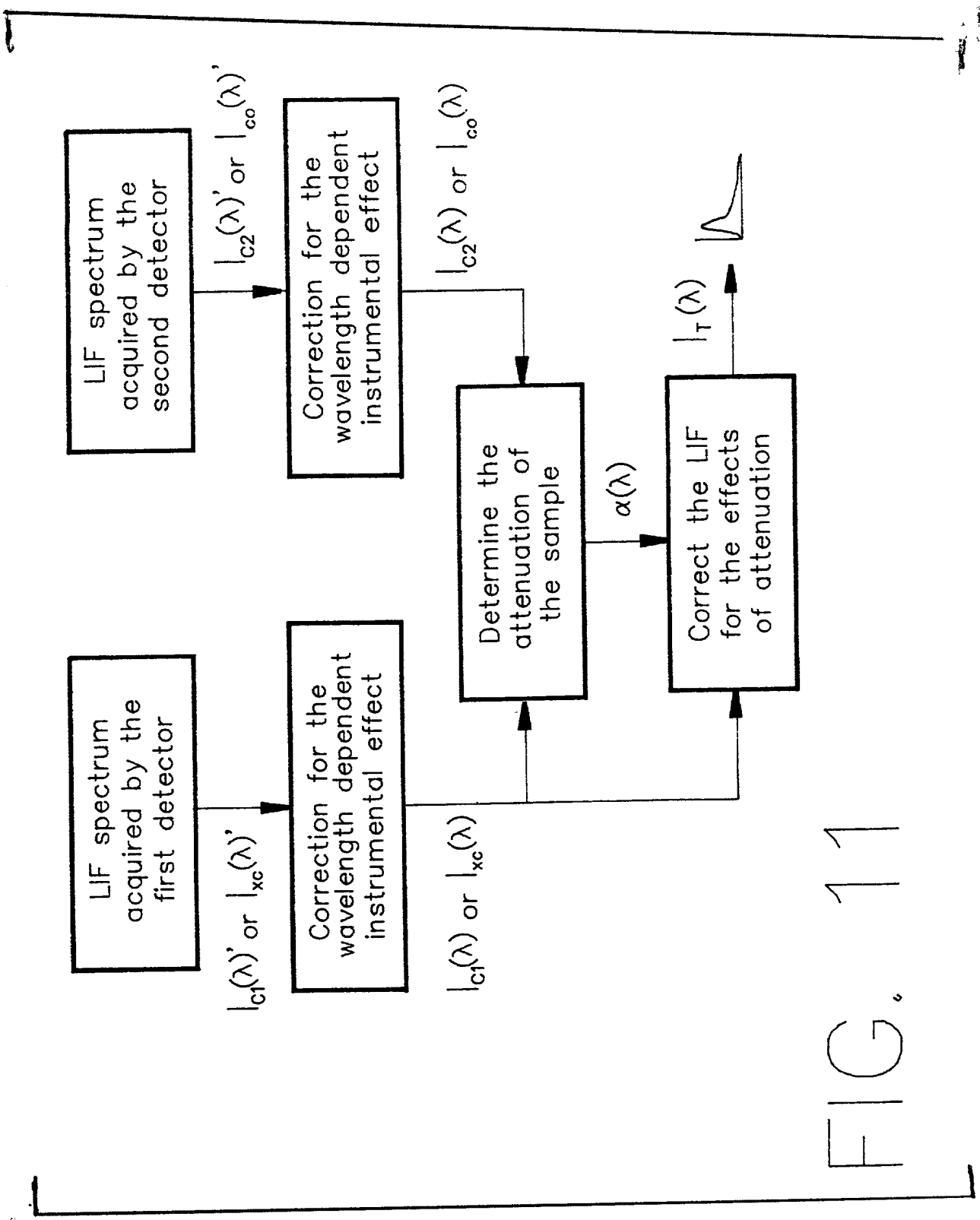

FIG. 11

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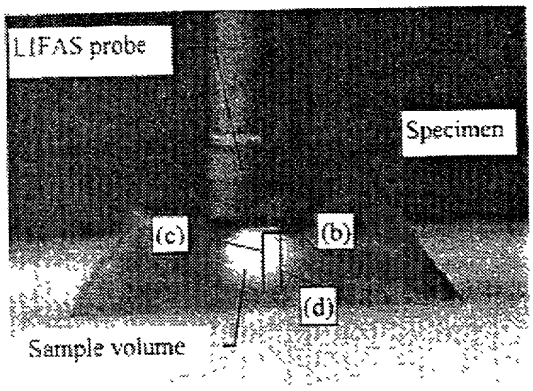
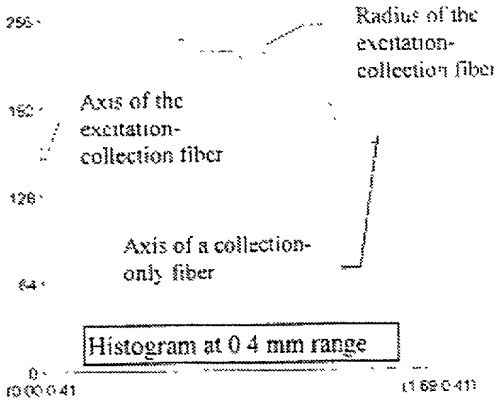
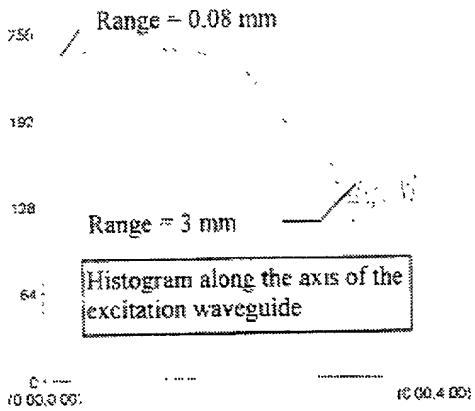


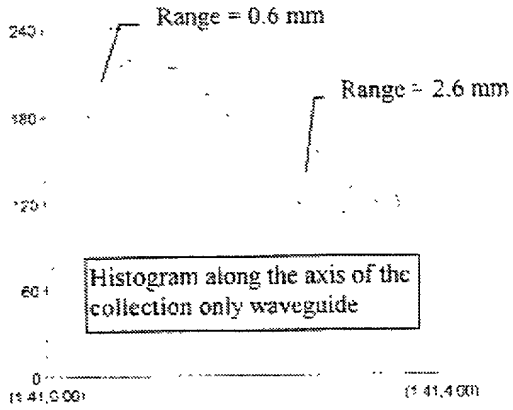
(a)



(b)



(c)



(d)

FIG. 12

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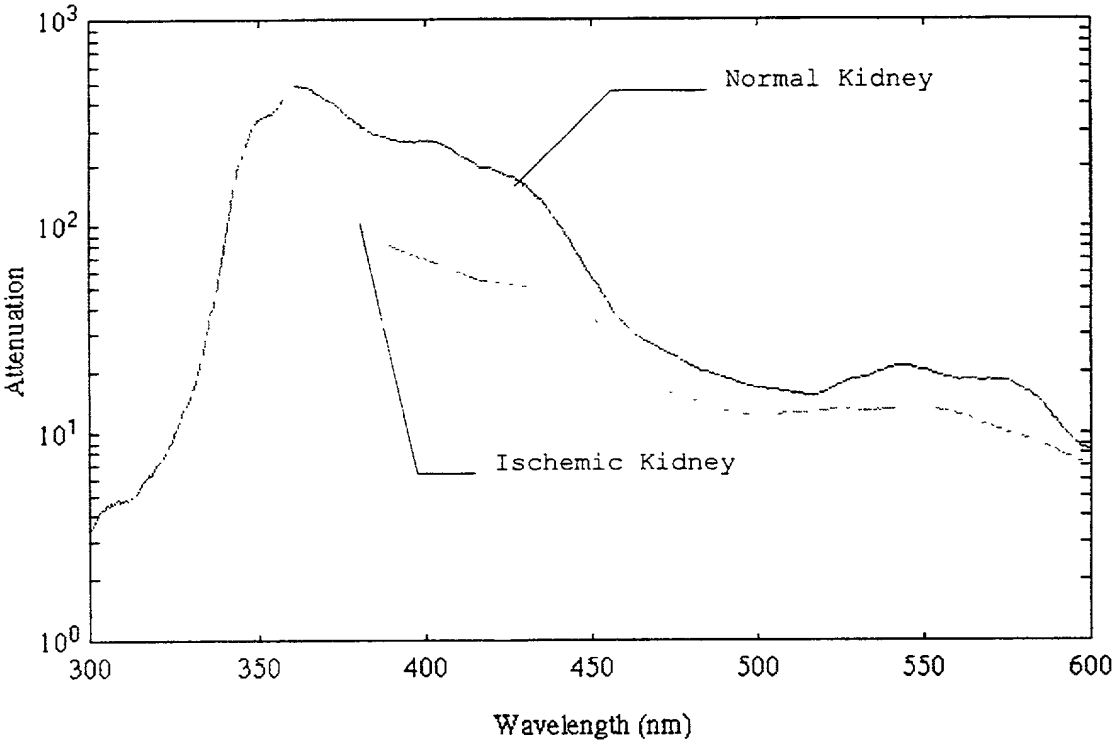
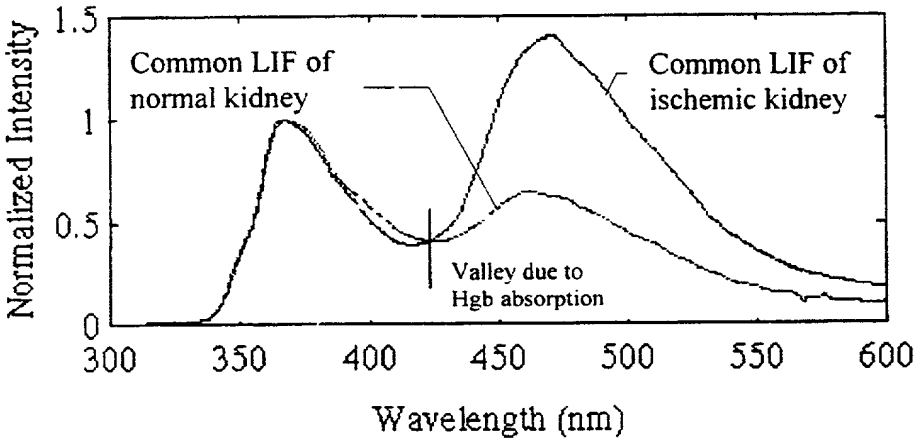
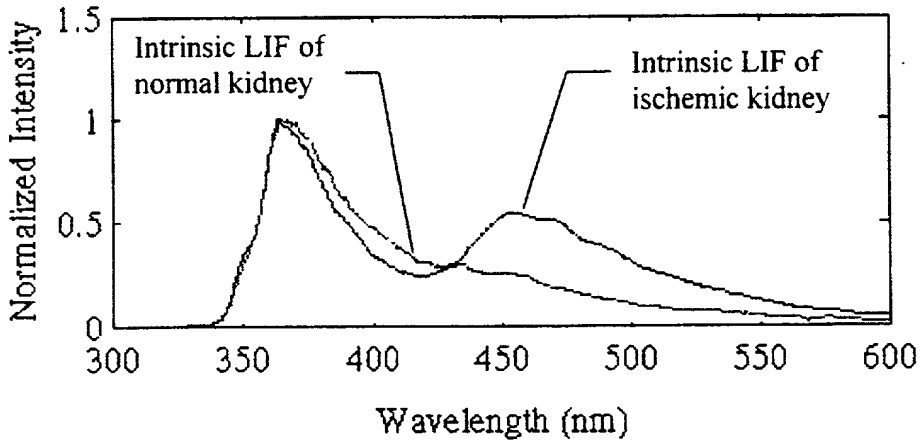


FIG. 13

CANCELED



(a)



(b)

FIG. 14

CANCELED

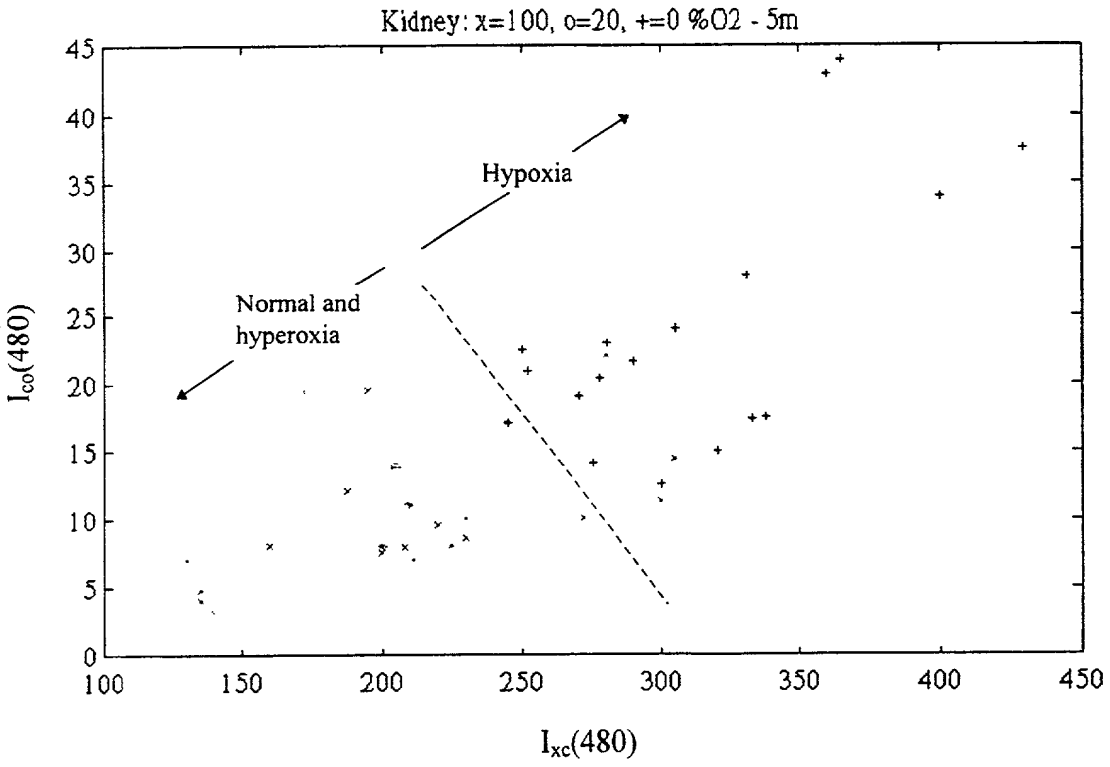


FIG. 15

CANCELED

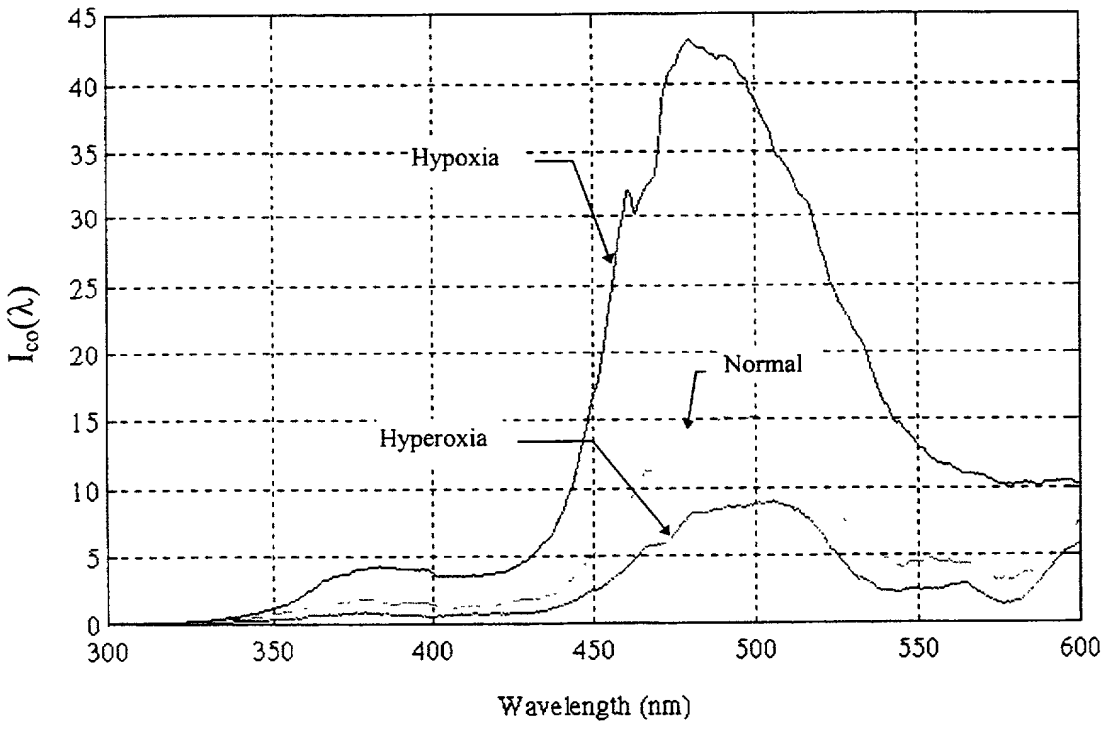


FIG. 16

CANCELED